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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/894,246	05/22/98	PERRICAUDET M	EX95001-US

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1630	13

DATE MAILED: 02/25/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/894,246	Perricaudet et al.
Examiner	**Group Art Unit**
Shin-Lin Chen	1633

☒ Responsive to communication(s) filed on *Dec 13, 1999*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *26-56* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *26-56* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *11*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

The amendment filed 12-13-99 (Paper No. 10) has been entered. Claims 27, 28, 31-33, 45, 46 and 49-51 have been amended. Claims 26-56 arepending.

Election/Restriction

The election of species requirement has been withdrawn.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 26-56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of decreasing CD4+, CD3+ and CD8+ T cells by the combination of anti-CD3 or anti-CD4 antibody with Ad-βgal-gp19K expressing gp19K protein of adenovirus, and decreasing cytotoxic activity of splenocytes, isolated from animals treated with anti-CD4 antibody and Ad-βgal-gp19K, on p815-β-gal target cells expressing β-galactosidase, does not reasonably provide enablement for a composition comprising any immunosuppressive agent and a recombinant adenovirus containing a therapeutic gene and any immunoprotective gene such as ICP47 gene and UL18 gene, and a method for expression of a therapeutic gene using said composition. The specification does not enable any person skilled in

the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 26-56 are directed to a composition comprising an immunosuppressive agent and a recombinant adenovirus expressing a therapeutic gene and an immunoprotective gene (e.g. gp19K) and a method for expression of said therapeutic gene comprising consecutively or simultaneously administering said immunosuppressive agent (e.g. CTLA4Ig) and said recombinant adenovirus into a subject.

Claims 26-56 encompass any immunosuppressive agent including cyclosporin, FK506, azathioprine, corticosteroids, a polyclonal antibody or a monoclonal antibody that is able to inactivate an immune molecule, and encompass any immunoprotective gene whose product acts on the activity of a major histocompatibility complex (MHC) or on the activity of a cytokine.

The specification of the present application only discloses decreasing CD4+, CD3+ and CD8+ T cells by the combination of anti-CD3 or anti-CD4 antibody with Ad-βgal-gp19K expressing gp19K protein of adenovirus, and decreasing cytotoxic activity of splenocytes, isolated from animals treated with anti-CD4 antibody and Ad-βgal-gp19K, on p815-β-gal target cells expressing β-galactosidase.

The specification (page 5) indicates that immunointervention strategies have been developed to create a permissive immune environment and to induce a state of tolerance with regard to predefined foreign antigen and it is precisely at this level that the present invention intervenes. Linsley et al., 1992 (U) reports that CTLA4Ig suppresses T cell-dependent antibody

responses to sheep red blood cells (SRBC) or keyhole limpet hemocyanin (KLH). Treatment with all dose of CTLA4Ig suppresses primary SRBC IgG1 antibody (Ab) responses in pooled sera by >95%. However, secondary Ab responses varied according to the dose of CTLA4Ig. Mice treated with 200 ug of CTLA4Ig show peak Ab responses that was suppressed ~80% in comparison to those of mice receiving a primary immunization. Mice treated with 100ug of CTLA4Ig do not show suppressed secondary responses, and those treated with 50ug of CTLA4Ig give accelerated response. Treatment with large doses (200ug) of CTLA4Ig leads to prolonged immunosuppression but not permanent tolerance of SRBCs although CTLA4Ig treatment induces long-term survival of pancreatic islet cell xenografts has been reported. The possible explanations for failing to induce tolerance in Linsley et al. study are (1) SRBCs and KLH are extremely potent immunogens, and inducing tolerance to them may require greater blocking of B7 or additional blocking of other costimulatory molecules; (2) certain T cell populations vary in their dependence on B7 costimulation for maintained responses. Linsley et al. suggests that virtually complete suppression (>95%) of *in vivo* immune responses by CTLA4Ig does not necessarily lead to tolerance (e.g. abstract, page 794). Further, the level of immunoprotective effect of a immunoprotective gene such as a gp19K, a ICP47, a UL18 gene and other unidentified immunoprotective genes may vary because of different mechanisms of their immunoprotective function. Kay et al., 1997 (PE) reports that although recombinant adenovirus vectors offer a very efficient means by which to transfer genetic information into cells *in vivo*, antigen-dependent immunity limits the duration of gene expression and prevents retreatment (e.g.

abstract). Therefore, the effectiveness to create a permissive immune environment and to induce a state of tolerance with regard to predefined foreign antigen depends on the potency of the antigen, the immunosuppressive agent and the immunoprotective gene used. A skilled person in the art would have to trial and error to determine which combination of an immunosuppressive agent and a immunoprotective gene would exhibit immunoprotective effect on the treated subject and prolong the expression of the therapeutic gene in said subject.

The specification fails to provide adequate guidance and fails to demonstrate how a composition comprising an immunosuppressive agent and a recombinant adenovirus containing a therapeutic gene and an immunoprotective gene protects a subject or an individual from challenge of an antigen other than the combination of anti-CD3 or anti-CD4 antibody with gp19K gene of adenovirus. The specification also fails to provide adequate guidance and fails to demonstrate how to express a therapeutic gene from an adenovirus comprising consecutively or simultaneously administering an immunosuppressive agent and a recombinant adenovirus containing a therapeutic gene and an immunoprotective gene. Thus, it would have required a skilled person in the art at the time of the invention undue experimentation to have practiced the full scope of the invention. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the absence of working examples and scarcity of guidance in the specification, and the unpredictable nature of the art.

The quantity of the experimentation required for the invention as claimed include identification of polyclonal Abs, monoclonal Abs which has immunosuppressant function, identification of immunoprotective gene, in addition to gp19 of adenovirus, ICP47 gene of herpes virus and UL18 gene of cytomegalovirus, which inhibits expression of the MHC proteins or antigen presentation, determination of protective function of said immunoprotective gene, and determination of protective function of the various combination of immunosuppressive agent and as adenovirus containing a therapeutic gene and an immunoprotective gene.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. The rejection of claims 26-56 under 35 U.S.C. 103(a) has been withdrawn.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian Stanton can be reached on (703) 308-2801. The fax phone number for this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.

JOHN L. LeGUYADER
PRIMARY EXAMINER
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